Status of Application, Amendments and/or Claims

Applicant's arguments, filed 15 September 2011, have been entered in full. Claims 1-45, 51-54, 56 are canceled. Claims 46-50, 55, 57-86 are pending and under examination.

Information Disclosure Statement

The information disclosure statement(s) (IDS) (filed 15 September 2011) was received and complies with the provisions of 37 CFR §§1.97, 1.98 and MPEP § 609. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-50, 55, 57-86 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pages 2-7 of the previous Office Action (15 June 2011).

Applicant discusses the Examiner's arguments from the previous Office Action. Applicant states that Taimr et al. (reference submitted by the Examiner) is cited for a

purported teaching of an opposite biological effect. Applicant states that the Office action argues that Taimr et al. teach that TRAIL agonists are useful as anti-fibrotic agents whereas the specification teaches that INSP035 (a TRAIL antagonist) is useful for the treatment of fibrosis. Applicant argues that Taimr et al. teach, based on in vitro data, that at high, non-physiological concentrations (1 ug/ml), exogenous TRAIL strongly induces apoptosis of activated stellate cells (Figures 5 and 7). Applicant contends that the authors conclude that a TRAIL agonist may be a good candidate for treating fibrosis by inducing apoptosis of activated hepatic stellate cells. Applicant argues that the results of Taimr et al. were confirmed by Yurovsky et al. (newly submitted reference by Applicant). Yurovsky et al. report that exogenous TRAIL strongly induces apoptotic cell death in lung fibroblast at concentrations of 100 ng/ml or higher. Applicant maintains that Yurovsky et al. also teach that at concentrations of 10 ng/ml or lower (more physiological levels of TRAIL) exogenous TRAIL stimulates fibroblast into extracellular matrix (ECM) production, notably collagen type I production. Applicant contends that this activity on ECM production appears to involve the TGF-beta pathway. Applicant states Yurovsky et al. teach physiological concentrations of TRAIL are estimated at about 1 ng/ml. Applicant states that Yurovsky et al. teaches, "..taken together, these data indicate that TRAIL, at doses below the apoptosis-inducing threshold, can upregulate ECM production by fibroblast. The mechanism of this stimulation likely involves triggering the TGF-beta pathway of autocrine and paracrine activation of fibroblast. If this process continues uncontrolled, it may contribute to the development of fibrosis, particularly in the lungs of patients with systemic sclerosis."

Applicant argues that the reference suggests the TRAIL/TGF-beta signaling pathway as a target for treating fibrosis in typical physiological settings. Applicant argues that the instant specification demonstrates that INSP035 polypeptide is capable of inhibiting exogenous TRAIL activity in vitro. Example 2 demonstrates that INSP035 is an inhibitor of TRAIL mediated apoptosis at TRAIL concentrations of about 2 ng/ml. Applicant maintains that from Yurovsky et al. it is known that at such concentrations, exogenous TRAIL induces collagen production in fibroblast. Applicant maintains, that based on the results presented in the instant specification and on the fact that TRAIL stimulates collagen production at low concentrations, the results teach one skilled in the art that INSP035 could be used to reduce collagen deposition mediated by TRAIL pathway and treat fibrotic disease. Applicant submits that there is no contradiction between the teaching of Taimr et al. and the instant specification. Applicant argues that Taimr et al. show, similar to the teachings of Yurovsky et al. that exogenous TRAIL at non physiological concentration induces apoptosis of activated stellate cells. The instant specifications shows that under physiological conditions, INSP035 is capable of counteracting TRAIL activities, related to collagen production.

Applicant's arguments have been fully considered but are not deemed persuasive. MPEP 2164.02 states that "correlation" refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working

examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate. The Examiner understands that the specification need not contain working examples, if disclosed in a manner where one skilled in the art could practice without undue experimentation. Lack of working examples is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. In the instant case, the art is unpredictable and the art does not teach the in vitro assays employed in the instant specification as art recognized in vivo models for fibrosis. Applicant argues that both Taimr and Yurovsky demonstrate that TRAIL at non physiological conditions induces apoptosis of certain cells. Taimr et al. teach apoptosis of hepatic stellate cells and Yurovsky et al. teach apoptosis of normal lung fibroblast. Taimr et al. teach that because activated stellate cells are responsible for the exuberant and unbalanced wound healing response in cirrhosis, their selective removal would be a potential mechanism to attenuate liver fibrosis. Taimr et al. teach that if TRAIL can induce selective apoptosis of activated stellate cells, it would become a candidate anti-fibrotic agent. Taimr et al. teach that their data suggests that TRAIL agonists could be used to reduce the number of activated stellate cells as a therapeutic approach to reduce fibrosis. Applicant argues Yurovsky et al. teach that TRAIL, at doses below the apoptosis-inducing threshold, can upregulate ECM production by fibroblast. The mechanism of this stimulation likely involves triggering the TGF-beta pathway of autocrine and paracrine activation of

fibroblast. If this process continues uncontrolled, it may contribute to the development of fibrosis, particularly in the lungs of patients with systemic sclerosis. Applicant argues that the reference suggests the TRAIL/TGF-beta signaling pathway as a target for treating fibrosis in typical physiological settings. Applicant argues that Example 2 demonstrates **that INSP035 is an inhibitor of TRAIL mediated apoptosis at TRAIL concentrations of 2 ng/ml** and that it is known that at such concentrations, exogenous TRAIL induces collagen production in fibroblast. The Examiner notes that the specification **fails to teach that INSP035 inhibits TRAIL mediated collagen production at TRAIL concentrations of 2 ng/ml.** The references (i.e. Taimr et al. and Yurovsky et al.) both demonstrate that TRAIL is a pleiotropic molecule which may or may not be acting a various signaling pathways for inducing fibrosis. Without employment of an art recognized animal model for fibrosis, it would have been unpredictable what effect SEQ ID NO: 2, 5, and 7, if any, would have when administered to a patient. For example, Power et al. (US Patent 7,638,480) teach an animal model for lung fibrosis (intra-tracheal injection bleomycin to mice). Power et al. teach that the administration of osteoprotegerin (OPG) reduced lung fibrosis (column 26, lines 9-51). It could not be predicted that the cell culture data presented in the instant specification would be in any way correlative with therapeutic agents for in vivo treatment of fibrotic diseases.

Applicant argues that the pending claims do not recite fragments and/or mutants of INSP03535 full length (SEQ ID NO:2) nor polypeptides having random mutations or deletions. Applicant argues that the claims recite polypeptides comprising or consisting

of SEQ ID NOs: 5 or 7, i.e. polypeptides comprising or consisting of definite sequences, shown to display similar activity as SEQ ID NO:2 on TRAIL inhibition in vitro. Applicant cites page 7, lines 18-22 and page 27, line 7. Applicant argues that Example 5 of the present invention describes an assay for testing the activity of INSP035 in bleomycin treated mice (mouse model of lung fibrosis). Applicant argues that polyhistidine labeled forms of SEQ ID NOs: 2, 5 and 7 have been demonstrated to inhibit TRAIL activity. Applicant cites Figure 1 and page 7, lines 18-22. Applicant argues that the Office Action compared the in vitro effects of INSP035 with those of leptin and concluded that it is no way predictable that mutations, deletions, etc. in the disclosed sequence would afford a protein having activity comparable to the one disclosed. Applicant argues that this argumentation is not applicable to the pending application and, as noted above, the present application, demonstrates that SEQ ID NOs: 5 and 7 have comparable activity to SEQ ID NO:2. Applicant argues that the as filed specification provides teaching as to who one is to administer the claimed polypeptides for the treatment of lung or liver fibrosis and provides teaching as to how one is to make the claimed polypeptides (SEQ ID NOs: 2, 5 and 7).

Applicant's arguments have been fully considered but are not found persuasive. The specification teaches the full length INSP035 as SEQ ID NO:2 (163 amino acids). The specification teaches the cDNA of INSP035 starting at the 2nd methionine called INSP035 medium form. The amino acid sequence is SEQ ID NO:5 (88 amino acids). The specification teaches a modified INSP035 medium form with an isoleucine substitution at position 1 as SEQ ID NO:7 (88 amino acids). Contrary to Applicant's

assertion, SEQ ID NO:5 and SEQ ID NO:7 would be considered fragments of SEQ ID NO:2 and SEQ ID NO:7 would be considered a mutant of SEQ ID NO:2. The Examiner understand that SEQ ID NOs: 5 and 7 display similar activity as SEQ ID NO:2 (i.e. inhibition of TRAIL induced apoptosis of fibroblasts in vitro). However, this is not tantamount to the claimed method of treating liver or lung fibrosis in a patient. The specification has not shown that SEQ ID NO:2 can be administered to treat fibrosis, thus it would be highly unpredictable that SEQ ID NOs: 5 or 7 can be administered to treat fibrosis in a subject.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to REGINA M. DEBERRY whose telephone number is (571)272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/R. M. D./
Examiner, Art Unit 1647
11/8/11

/Elizabeth C. Kemmerer/
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